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SEARCH REQUEST FORM

56890

Scientific and Technical Information Center

Requester's Full Name: PATEL SUDHAKER Examiner #: 77018 Date: 12/18/01
Art Unit: 1624 Phone Number 30 84709 Serial Number: 09912163
Mail Box and Bldg/Room Location: CM1 4E17 Results Format Preferred (circle): PAPER DISK E-MAIL
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If more than one search is submitted, please prioritize searches in order of need. MEP

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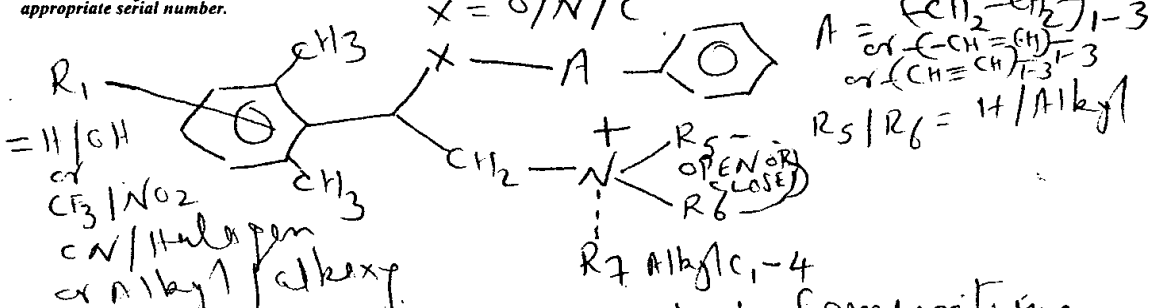
Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: PHENYL & PHENYLALKYL-SUBSTITUTED ETHANOLAMINES & ETHYLENEDIAMINES

Inventors (please provide full names): KLAUS FUCHS et al

Earliest Priority Filing Date: 8/18/2000

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*



Need inf @ compounds & Compositions & use for treatment of diseases related to OVERSTIMULATION of NE, brain trauma.
Also synthetic process of making gels
see claims 25-29
copy of claims ended

THF
1624

POINT OF CONTACT:
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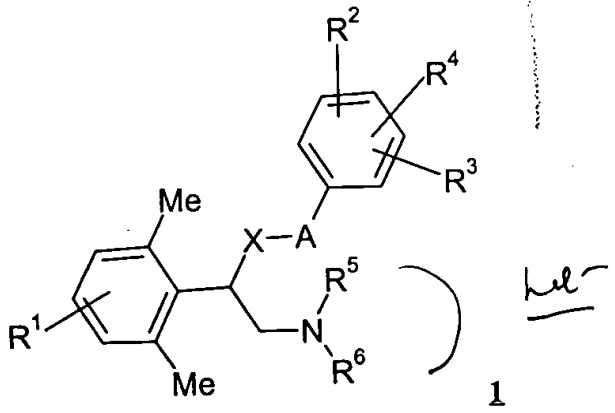
PTO-1590 (8-01)

We Claim:

1. A compound of formula 1,



1

wherein:

R^1 is hydrogen, hydroxy, CF_3, NO_2, CN, halogen, C_1-C_8-alkyl, or C_1-C_8-alkoxy;

R^2, R^3, and R^4 independently of one another are hydrogen, C_1-C_8-alkyl, hydroxy, NO_2, CN, C_1-C_8-alkyloxy, CF_3, or halogen;

R^5 and R^6 independently of one another are hydrogen or a group consisting of C_1-C_8-alkyl, C_2-C_8-alkenyl, C_3-C_8-alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-C_1-C_6-alkylene, C_5-C_8-cycloalkenyl, C_5-C_8-cycloalkenyl-C_1-C_6-alkylene, C_6-C_{10}-aryl, and C_6-C_{10}-aryl-C_1-C_6-alkylene, each optionally substituted by a group consisting of C_1-C_6-alkyl, C_2-C_6-alkenyl, halogen, C_1-C_6-alkyloxy, $-NH_2$, $-NH(C_1$-C_4-alkyl), $-N(C_1$-C_4-alkyl)$_2$, hydroxy, =O, -COOH, $-CO-OC_1$-C_4-alkyl, $-CONH_2$, $-CONH(C_1$-C_4-alkyl), $-CON(C_1$-C_4-alkyl)$_2$, and CF_3, or

R^5 and R^6 together with the nitrogen atom are a saturated or unsaturated 5-, 6-, 7-, or 8-membered heterocyclic group optionally containing one or two further heteroatoms consisting of sulfur, oxygen, and nitrogen, and optionally mono-, di-, or trisubstituted by a group consisting of C_1-C_4-alkyl, hydroxy, =O, -COOH, $-CO-OC_1$-C_4-alkyl, $-CONH_2$, $-CONH(C_1$-C_4-alkyl), $-CON(C_1$-C_4-alkyl)$_2$, halogen, and benzyl;

X is oxygen, -NH-, -N(CHO)-, $-N(CO-C_1$-C_6-alkyl), $-N(C_1$-C_6-alkyl), or $-N(C_3$-C_6-cycloalkyl-C_1-C_4-alkylene); and

A is a group consisting of C_1-C_6-alkylene, C_2-C_6-alkenylene, and C_3-C_6-alkynylene, each optionally substituted by a group consisting of halogen, =O, and hydroxy,

or an optical isomer, enantiomer, tautomer, free base, or pharmacologically acceptable acid addition salt thereof.

2. The compound of formula **1** according to claim 1, wherein:

R^1 is hydrogen, halogen, C_1-C_6-alkyl, CF_3, or methoxy;

R^2, R^3, and R^4 independently of one another are hydrogen, C_1-C_6-alkyl, C_1-C_6-alkyloxy, CF_3, or halogen;

R^5 and R^6 independently of one another are hydrogen or a group consisting of C_1-C_6-alkyl, C_2-C_6-alkenyl, C_3-C_6-alkynyl, C_3-C_6-cycloalkyl, C_3-C_6-cycloalkyl-C_1-C_6-alkylene, C_5-C_6-cycloalkenyl, C_5-C_6-cycloalkenyl-C_1-C_6-alkylene, phenyl, and phenyl-C_1-C_6-alkylene, each optionally substituted by a group consisting of C_1-C_4-alkyl, C_2-C_4-alkenyl, halogen, C_1-C_4-alkyloxy, hydroxy, -$CONH_2$, =O, and CF_3, or

R^5 and R^6 together with the nitrogen atom are a saturated or unsaturated 5-, 6-, or 7-membered heterocyclic group optionally containing one or two further heteroatoms consisting of sulfur, oxygen, and nitrogen and optionally mono-, di-, or trisubstituted by C_1-C_4-alkyl, hydroxy, or -$CONH_2$;

X is oxygen, -NH-, -N(CHO)-, -N(CO-C_1-C_5-alkyl), -N(C_1-C_5-alkyl), or -N(C_3-C_6-cycloalkyl-C_1-C_4-alkylene); and

A is C_1-C_5-alkylene, C_2-C_4-alkenylene, or C_3-C_4-alkynylene,

or an optical isomer, enantiomer, tautomer, free base, or pharmacologically acceptable acid addition salt thereof.

3. The compound of formula **1** according to claim 2, wherein:

R^1 is hydrogen, C_1-C_4-alkyl, or CF_3;

R^2, R^3, and R^4 independently of one another are hydrogen, C_1-C_4-alkyl, CF_3, or halogen;

R^5 and R^6 independently of one another are hydrogen, C_1-C_6-alkyl, CF_3-C_1-C_6-alkylene, C_2-C_6-alkenyl, C_3-C_6-alkynyl, C_3-C_6-cycloalkyl, C_3-C_6-cycloalkyl-C_1-C_6-alkylene, cyclohexenyl, cyclohexenyl-C_1-C_6-alkylene, propenyl-cyclohexenylene-C_1-C_6-alkylene, phenyl, or phenyl-C_1-C_6-alkylene, or

R^5 and R^6 together with the nitrogen atom are a saturated or unsaturated 5-, 6-, or 7-membered heterocyclic group optionally containing another nitrogen atom and optionally mono-, di-, or trisubstituted by C_1-C_4-alkyl, hydroxy, or -$CONH_2$;

X is oxygen, -NH-, -N(CHO)-, -N(CO-methyl), -N(CO-ethyl), -N(C_1-C_5-alkyl), or -N(C_3-C_6-cycloalkyl-methylene); and

A is -CH_2-, -CH_2-CH_2-, or -CH_2-CH_2-CH_2-,

or an optical isomer, enantiomer, tautomer, free base, or pharmacologically acceptable acid addition salt thereof.

4. A compound of formula **1** according to claim 3, wherein

R^1 is hydrogen or methyl;

R^2 and R^3 independently of one another are hydrogen, methyl, fluorine, chlorine, or bromine;

R^4 is hydrogen, fluorine, chlorine, or bromine;

R^5 and R^6 independently of one another are hydrogen, C_1-C_6-alkyl, CF_3-C_1-C_6-alkylene, C_2-C_6-alkenyl, C_3-C_6-cycloalkyl, cyclohexyl, C_3-C_6-cycloalkyl-C_1-C_6-alkylene, cyclohexenyl, cyclohexenyl-C_1-C_6-alkylene, or

R^5 and R^6 together with the nitrogen atom are a heterocyclic group consisting of pyrrolidine, piperidine, 1,2,3,6-tetrahydropyridine, and azepan;

X oxygen, -NH-, -N(CHO)-, -N(CO-methyl), -N(CO-ethyl), -N(methyl), -N(ethyl), -N(propyl), -N(butyl), -N(pentyl), or -N(cyclopropylmethylene); and

A is -CH_2-, -CH_2-CH_2-, or -CH_2-CH_2-CH_2-,

or an optical isomer, enantiomer, tautomer, free base, or pharmacologically acceptable acid addition salt thereof.

5. The compound of formula **1** according to claim 4, wherein:

R^5 and R^6 independently of one another are hydrogen, methyl, propyl, butyl, hexyl, cyclopropylmethyl, or cyclohexenemethyl, or

R^5 and R^6 together with the nitrogen atom are a heterocyclic group consisting of pyrrolidine, piperidine, 1,2,3,6-tetrahydropyridine, and azepan; and

X is oxygen, -NH-, -N(CHO)-, -N(CO-methyl), -N(CO-ethyl), -N(ethyl), -N(propyl), -N(butyl), -N(pentyl), or -N(cyclopropylmethylene),

or an optical isomer, enantiomer, tautomer, free base, or pharmacologically acceptable acid addition salt thereof.

6. The compound of formula **1** according to claim 4, wherein:

R^2 and R^3 independently of one another are hydrogen or fluorine;

R^4 is hydrogen;

R^5 and R^6 independently of one another are hydrogen, butyl, hexyl, or cyclohexenemethyl, or

R^5 and R^6 together with the nitrogen atom are piperidine and 1,2,3,6-tetrahydropyridine;

X is oxygen or -NH-; and

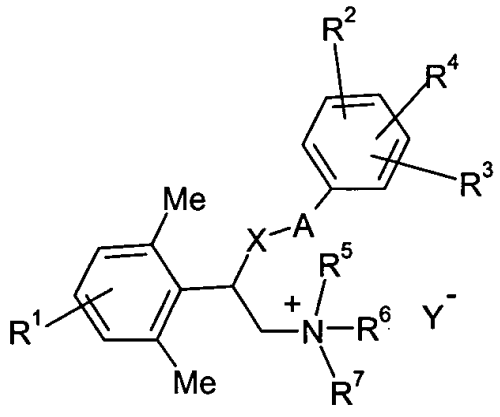
A is $-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-$,

or an optical isomer, enantiomer, tautomer, free base, or pharmacologically acceptable acid addition salt thereof.

7. A compound of formula **1** according to one of claims 1 to 6, wherein R^1 is hydrogen and R^2 and R^3 are in the *ortho* position with respect to each other.

8. A compound of formula **1** according to one of claims 1 to 6, wherein R^1 is methyl and R^2 and R^3 are in the *ortho* position with respect to each other.

9. A quaternary ammonium compound of formula **1-Y**



1-Y

wherein:

R^1 is hydrogen, hydroxy, CF_3, NO_2, CN, halogen, C_1-C_8-alkyl, or C_1-C_8-alkoxy;

R^2, R^3, and R^4 independently of one another are hydrogen, C_1-C_8-alkyl, hydroxy, NO_2, CN, C_1-C_8-alkyloxy, CF_3, or halogen;

R^5 and R^6 independently of one another are a group consisting of C_1-C_8-alkyl, C_2-C_8-alkenyl, C_3-C_8-alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-C_1-C_6-alkylene, C_5-C_8-cycloalkenyl, C_5-C_8-cycloalkenyl-C_1-C_6-alkylene, C_6-C_{10}-aryl, and C_6-C_{10}-aryl-C_1-C_6-alkylene, each optionally substituted by a group consisting of C_1-C_6-alkyl, C_2-C_6-alkenyl, halogen, C_1-

C_6-alkyloxy, $-NH_2$, $-NH(C_1-C_4\text{-alkyl})$, $-N(C_1-C_4\text{-alkyl})_2$, hydroxy, =O, -COOH, $-CO-OC_1-C_4$-alkyl, $-CONH_2$, $-CONH(C_1-C_4\text{-alkyl})$, $-CON(C_1-C_4\text{-alkyl})_2$, and CF_3, or

R^5 and R^6 together with the nitrogen atom are a saturated or unsaturated 5-, 6-, 7-, or 8-membered heterocyclic group optionally containing one or two further heteroatoms consisting of sulfur, oxygen, and nitrogen, and optionally mono-, di-, or trisubstituted by a group consisting of C_1-C_4-alkyl, hydroxy, =O, -COOH, $-CO-OC_1-C_4$-alkyl, $-CONH_2$, $-CONH(C_1-C_4\text{-alkyl})$, $-CON(C_1-C_4\text{-alkyl})_2$, halogen, and benzyl;

R^7 is C_1-C_4-alkyl;

X is oxygen, -NH-, -N(CHO)-, $-N(CO-C_1-C_6\text{-alkyl})$, $-N(C_1-C_6\text{-alkyl})$, or $-N(C_3-C_6\text{-cycloalkyl-}C_1-C_4\text{-alkylene})$; and

Y^- is a halide group;

A is a group consisting of C_1-C_6-alkylene, C_2-C_6-alkenylene, and C_3-C_6-alkynylene, each optionally substituted by a group consisting of halogen, =O, and hydroxy,

or an optical isomer, enantiomer, tautomer, free base, or pharmacologically acceptable acid addition salt thereof.

10. The compound of formula **1-Y** according to claim 9, wherein:

R^1 is hydrogen, halogen, C_1-C_6-alkyl, CF_3, or methoxy;

R^2, R^3, and R^4 independently of one another are hydrogen, C_1-C_6-alkyl, C_1-C_6-alkyloxy, CF_3, or halogen;

R^5 and R^6 independently of one another are a group consisting of C_1-C_6-alkyl, C_2-C_6-alkenyl, C_3-C_6-alkynyl, C_3-C_6-cycloalkyl, $C_3-C_6\text{-cycloalkyl-}C_1-C_6$-alkylene, C_5-C_6-cycloalkenyl, $C_5-C_6\text{-cycloalkenyl-}C_1-C_6$-alkylene, phenyl, and phenyl-C_1-C_6-alkylene, each optionally substituted by a group consisting of C_1-C_4-alkyl, C_2-C_4-alkenyl, halogen, C_1-C_4-alkyloxy, hydroxy, $-CONH_2$, =O, and CF_3, or

R^5 and R^6 together with the nitrogen atom are a saturated or unsaturated 5-, 6-, or 7-membered heterocyclic group optionally containing one or two further heteroatoms consisting of sulfur, oxygen, and nitrogen and optionally mono-, di-, or trisubstituted by C_1-C_4-alkyl, hydroxy, or $-CONH_2$;

X is oxygen, -NH-, -N(CHO)-, $-N(CO-C_1-C_5\text{-alkyl})$, $-N(C_1-C_5\text{-alkyl})$, or $-N(C_3-C_6\text{-cycloalkyl-}C_1-C_4\text{-alkylene})$; and

A is C_1-C_5-alkylene, C_2-C_4-alkenylene, or C_3-C_4-alkynylene,

or an optical isomer, enantiomer, or tautomer thereof.

11. The compound of formula **1-Y** according to claim 10, wherein:

R^1 is hydrogen, C_1-C_4-alkyl, or CF_3;

R^2, R^3, and R^4 independently of one another are hydrogen, C_1-C_4-alkyl, CF_3, or halogen;

R^5 and R^6 independently of one another are C_1-C_6-alkyl, CF_3-C_1-C_6-alkylene, C_2-C_6-alkenyl, C_3-C_6-alkynyl, C_3-C_6-cycloalkyl, C_3-C_6-cycloalkyl-C_1-C_6-alkylene, cyclohexenyl, cyclohexenyl-C_1-C_6-alkylene, propenyl-cyclohexenylene-C_1-C_6-alkylene, phenyl, or phenyl-C_1-C_6-alkylene, or

R^5 and R^6 together with the nitrogen atom are a saturated or unsaturated 5-, 6-, or 7-membered heterocyclic group optionally containing another nitrogen atom and optionally mono-, di-, or trisubstituted by C_1-C_4-alkyl, hydroxy, or -$CONH_2$;

X is oxygen, -NH-, -N(CHO)-, -N(CO-methyl), -N(CO-ethyl), -N(C_1-C_5-alkyl), or -N(C_3-C_6-cycloalkyl-methylene); and

A is -CH_2-, -CH_2-CH_2-, or -CH_2-CH_2-CH_2-,

or an optical isomer, enantiomer, or tautomer thereof.

12. The compound of formula **1-Y** according to claim 11, wherein:

R^1 is hydrogen;

R^2 and R^3 independently of one another are hydrogen, methyl, fluorine, chlorine, or bromine;

R^4 is hydrogen, fluorine, chlorine, or bromine;

R^5 and R^6 independently of one another are C_1-C_6-alkyl, CF_3-C_1-C_6-alkylene, C_2-C_6-alkenyl, C_3-C_6-cycloalkyl, cyclohexyl, C_3-C_6-cycloalkyl-C_1-C_6-alkylene, cyclohexenyl, cyclohexenyl-C_1-C_6-alkylene, or

R^5 and R^6 together with the nitrogen atom are a heterocyclic group consisting of pyrrolidine, piperidine, 1,2,3,6-tetrahydropyridine, and azepan;

X oxygen, -NH-, -N(CHO)-, -N(CO-methyl), -N(CO-ethyl), -N(methyl), -N(ethyl), -N(propyl), -N(butyl), -N(pentyl), or -N(cyclopropylmethylene); and

A is -CH_2-, -CH_2-CH_2-, or -CH_2-CH_2-CH_2-,

or an optical isomer, enantiomer, or tautomer thereof.

13. The compound of formula **1-Y** according to claim 12, wherein:

R^5 and R^6 independently of one another are methyl, propyl, butyl, hexyl, cyclopropylmethyl, or cyclohexenemethyl, or

R^5 and R^6 together with the nitrogen atom are a heterocyclic group consisting of pyrrolidine, piperidine, 1,2,3,6-tetrahydropyridine, and azepan; and

X is oxygen, -NH-, -N(CHO)-, -N(CO-methyl), -N(CO-ethyl), -N(ethyl), -N(propyl), -N(butyl), -N(pentyl), or -N(cyclopropylmethylene),

or an optical isomer, enantiomer, or tautomer thereof.

14. The compound of formula **1-Y** according to claim 12, wherein:

R^2 and R^3 independently of one another are hydrogen or fluorine;

R^4 is hydrogen;

R^5 and R^6 independently of one another are butyl, hexyl, or cyclohexenemethyl, or

R^5 and R^6 together with the nitrogen atom are piperidine and 1,2,3,6-tetrahydropyridine;

X is oxygen or -NH-; and

A is $-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-$,

or an optical isomer, enantiomer, or tautomer thereof.

15. A compound of formula **1-Y** according to one of claims 9 to 14 wherein R^1 is hydrogen and R^2 and R^3 are in the *ortho* position with respect to each other.

16. A compound of formula **1-Y** according to one of claims 9 to 14 wherein R^1 is methyl and R^2 and R^3 are in the *ortho* position with respect to each other.

17. A pharmaceutical composition comprising an effective amount of a compound of formula **1** according to one of claims 1 to 8 and a conventional excipient or carrier.

18. A pharmaceutical composition comprising an effective amount of a compound of formula **1-Y** according to one of claims 9 to 16 and a conventional excipient or carrier.

19. A method for treatment or prophylaxis of functional disorders caused by overstimulation, in a host in need of such treatment or prophylaxis, which method comprises administering the host an effective amount of a compound of formula **1** according to one of claims 1 to 8.

20. A method for treatment or prophylaxis of functional disorders caused by overstimulation, in a host in need of such treatment or prophylaxis, which method comprises administering the host an effective amount of a compound of formula **1-Y** according to one of claims 9 to 16.

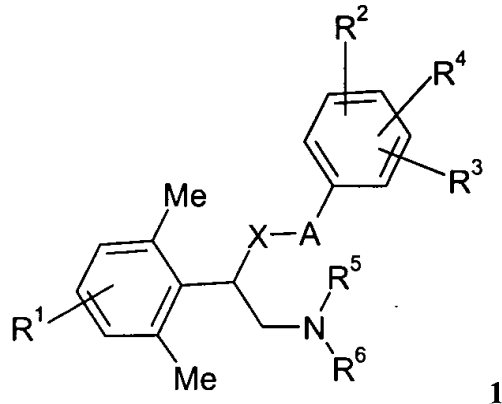
21. A method for treatment or prophylaxis of arrhythmias, spasms, cardiac and cerebral ischemias, pain, and neurodegenerative disorders, in a host in need of such treatment or prophylaxis, which method comprises administering the host an effective amount of a compound of formula **1** according to one of claims 1 to 8.

22. A method for treatment or prophylaxis of arrhythmias, spasms, cardiac and cerebral ischemias, pain, and neurodegenerative disorders, in a host in need of such treatment or prophylaxis, which method comprises administering the host an effective amount of a compound of formula **1-Y** according to one of claims 9 to 16.

23. A method for treatment or prophylaxis of epilepsy, hypoglycemia, hypoxia, anoxia, brain trauma, brain edema, cerebral stroke, perinatal asphyxia, degeneration of the cerebellum, amyotrophic lateral sclerosis, Huntington's disease, Alzheimer's disease, Parkinson's disease, cyclophrenia, hypotonia, cardiac infarct, heart rhythm disorders, angina pectoris, chronic pain, neuropathic pain and local anesthesia, in a host in need of such treatment or prophylaxis, which method comprises administering the host an effective amount of a compound of formula **1** according to one of claims 1 to 8.

24. A method for treatment or prophylaxis of epilepsy, hypoglycemia, hypoxia, anoxia, brain trauma, brain edema, cerebral stroke, perinatal asphyxia, degeneration of the cerebellum, amyotrophic lateral sclerosis, Huntington's disease, Alzheimer's disease, Parkinson's disease, cyclophrenia, hypotonia, cardiac infarct, heart rhythm disorders, angina pectoris, chronic pain, neuropathic pain and local anesthesia, in a host in need of such treatment or prophylaxis, which method comprises administering the host an effective amount of a compound of formula **1-Y** according to one of claims 9 to 16.

25. A method for making the compound of formula **1** according to one of claims 1 to 9



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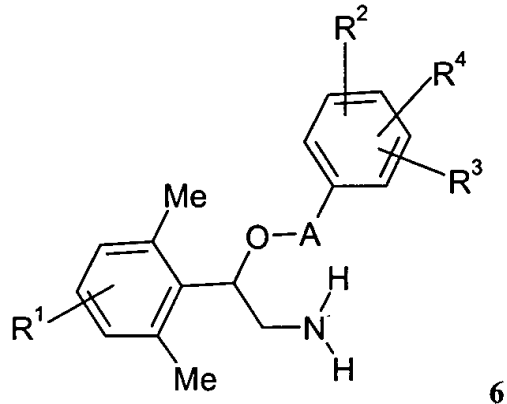
wherein the groups A, R^1, R^2, R^3, R^4, R^5, and R^6 have the meanings given in the respective claims 1 to 9 and wherein X is oxygen, the process comprising:

(a) reacting a compound of formula 6



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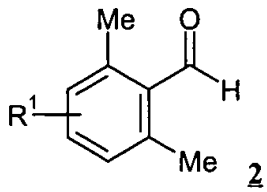
wherein the groups A, R^1, R^2, R^3, and R^4 have the meanings given above, in an organic solvent in the presence of an inorganic or organic base with a suitable alkylating agent having an alkyl group of R^5 and R^6 given above, to obtain a compound of formula 1, or

(b) converting an amine of formula 6 into a compound of formula 1 by reductive amination with a suitable carbonyl compound in the presence of a reducing agent.

26. The method according to claim 25, wherein the compound of formula 6 is made by:

(a) taking up a compound of formula 2



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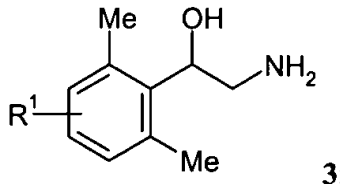
wherein R^1 has the meaning given in the respective claims 1 to 9, in trimethylsilylcyanide in a in the presence of a Lewis acid;

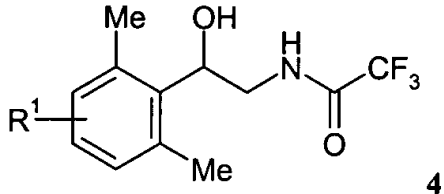
(b) diluting the resulting mixture using a suitable anhydrous organic solvent;

(c) reducing the diluted compound by means of a suitable reducing agent to form a compound of formula **3**



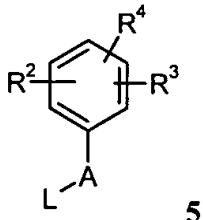
3;

(d) reacting the product of the previous step with trifluoroacetic acid anhydride, optionally after separation of the enantiomers, by taking up in a suitable organic solvent in the presence of a suitable organic or inorganic base, to form a compound of formula **4**



4; and

(e) dissolving the product of the previous step in a suitable organic solvent and reacting it in the presence of a suitable organic base with a compound of formula **5**



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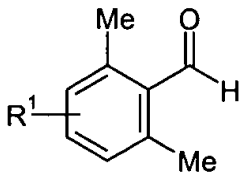
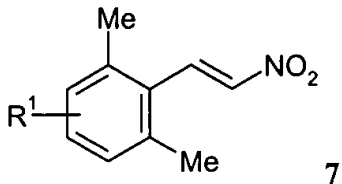
optionally dissolved in a suitable organic solvent, wherein the groups R^2, R^3, and R^4 have the meanings given in the respective claims 1 to 9, to form a compound of formula **6**.

27. The method according to claim 25, wherein the compound of formula **6** is obtained by reacting a compound of formula **2**



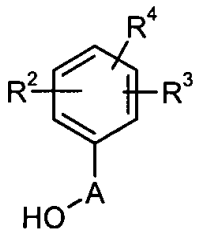
2

wherein R^1 has the meaning given in the respective claims 1 to 9, in a first step, using nitromethane in glacial acetic acid at elevated temperature, to obtain a compound of formula 7



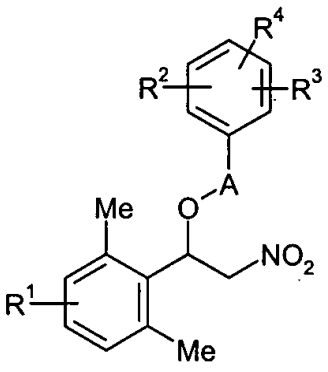
7

which is reacted in a suitable organic solvent by means of an alcohol 8



8

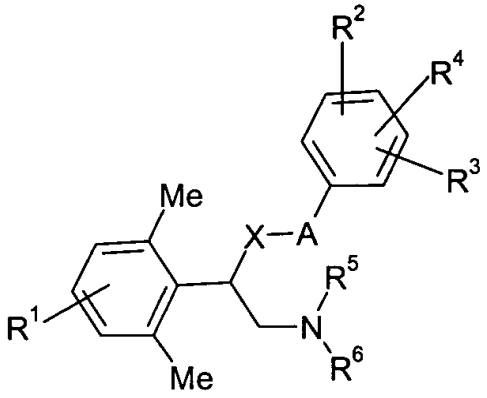
wherein the groups R^2, R^3, and R^4 have the meanings given in the respective claims 1 to 9, in the presence of a suitable base, to obtain an ether of formula 9



9

from which the compound of formula 6 may be obtained reductively, preferably by metal-catalyzed reduction.

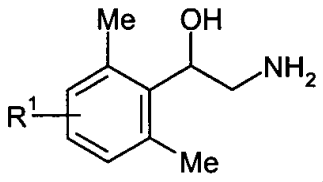
28. A method for preparing compounds of formula 1 according to one of claims 1 to 9



1

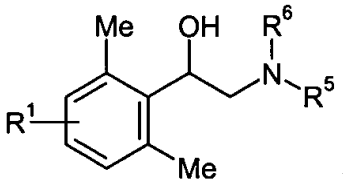
wherein the groups A, R^1, R^2, R^3, R^4, R^5, and R^6 have the meanings given in the respective claims 1 to 9 and wherein X is -NH-, the method comprising:

(a) reacting a compound of formula 3



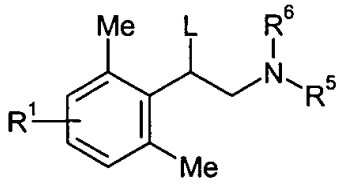
3

wherein the group R^1 has the meaning given in the respective claim 1 to 9, in a suitable organic solvent in the presence of a suitable inorganic or organic base using a suitable alkylating agent wherein the alkyl group has the definitions given in the respective claims 1 to 9 for R^5 and R^6, to obtain a compound of formula 16



16;

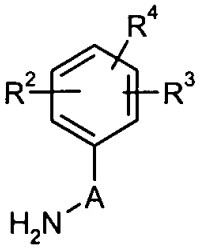
(b) reacting the product of the previous step, if R^5 or R^6 is hydrogen, using suitable protecting groups, by means of suitable halogenating reagents, suitable sulfonic acid chlorides, or suitable sulfonic acid anhydrides in the presence of suitable bases in suitable inert solvents to obtain a compound of formula 17



17

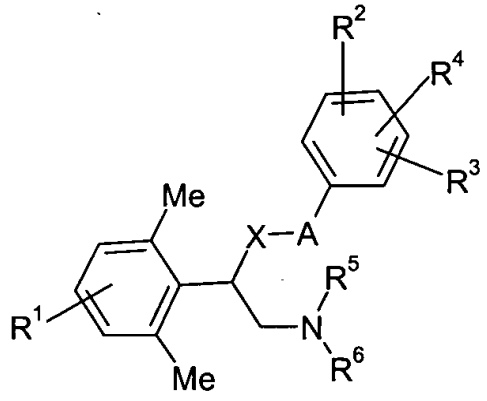
wherein L is a leaving group selected from chlorine, bromine, iodine, methanesulfonate, trifluoromethanesulfonate, and *p*-toluenesulfonate; and

(c) reacting the product of the previous step in a suitable organic solvent in the presence of a suitable inorganic or organic base using a compound of formula **18**



wherein the groups R^2, R^3, and R^4 have the meanings given in the respective claims 1 to 9, to obtain a compound of formula **1**.

29. A process for preparing a compound of formula **1**,

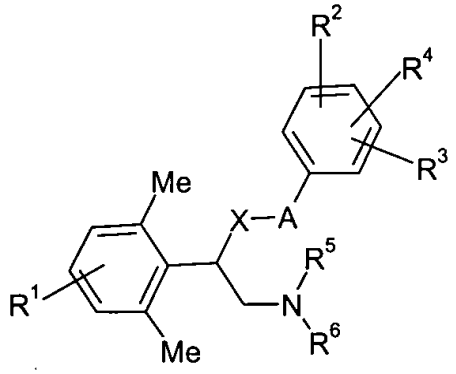


1

wherein the groups A, R^1, R^2, R^3, R^4, R^5, and R^6 have the meanings given in the respective claims 1 to 9 and wherein X denotes a group selected from -N(CHO)-, -N(CO-C_1-C_6-alkyl)-, -N(C_1-C_6-alkyl)- and -N(C_3-C_6-cycloalkyl-C_1-C_4-alkylene), the process comprising reacting a compound of formula **1** wherein X is -NH- is reacted in a suitable organic solvent in the presence of a suitable inorganic or organic base by means of a suitable alkylating, formylating, or acylating agent.

Abstract

Compounds of formula **1**,



1

wherein:

R^1 is hydrogen, hydroxy, CF_3, NO_2, CN, halogen, C_1-C_8-alkyl, or C_1-C_8-alkoxy;

R^2, R^3, and R^4 independently of one another are hydrogen, C_1-C_8-alkyl, hydroxy, NO_2, CN, C_1-C_8-alkyloxy, CF_3, or halogen;

R^5 and R^6 independently of one another are hydrogen or a group consisting of C_1-C_8-alkyl, C_2-C_8-alkenyl, C_3-C_8-alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-C_1-C_6-alkylene, C_5-C_8-cycloalkenyl, C_5-C_8-cycloalkenyl-C_1-C_6-alkylene, C_6-C_{10}-aryl, and C_6-C_{10}-aryl-C_1-C_6-alkylene, each optionally substituted by a group consisting of C_1-C_6-alkyl, C_2-C_6-alkenyl, halogen, C_1-C_6-alkyloxy, $-NH_2$, $-NH(C_1$-C_4-alkyl), $-N(C_1$-C_4-alkyl)$_2$, hydroxy, =O, -COOH, $-CO-OC_1$-C_4-alkyl, $-CONH_2$, $-CONH(C_1$-C_4-alkyl), $-CON(C_1$-C_4-alkyl)$_2$, and CF_3, or

R^5 and R^6 together with the nitrogen atom are a saturated or unsaturated 5-, 6-, 7-, or 8-membered heterocyclic group optionally containing one or two further heteroatoms consisting of sulfur, oxygen, and nitrogen, and optionally mono-, di-, or trisubstituted by a group consisting of C_1-C_4-alkyl, hydroxy, =O, -COOH, $-CO-OC_1$-C_4-alkyl, $-CONH_2$, $-CONH(C_1$-C_4-alkyl), $-CON(C_1$-C_4-alkyl)$_2$, halogen, and benzyl;

X is oxygen, -NH-, -N(CHO)-, $-N(CO-C_1$-C_6-alkyl), $-N(C_1$-C_6-alkyl), or $-N(C_3$-C_6-cycloalkyl-C_1-C_4-alkylene); and

A is a group consisting of C_1-C_6-alkylene, C_2-C_6-alkenylene, and C_3-C_6-alkynylene, each optionally substituted by a group consisting of halogen, =O, and hydroxy,

or an optical isomer, enantiomer, tautomer, free base, or pharmacologically acceptable acid addition salt thereof; methods of making such compounds; pharmaceutical compositions thereof, and their use in treating or preventing certain diseases.

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=> d que 18
L5                  STR
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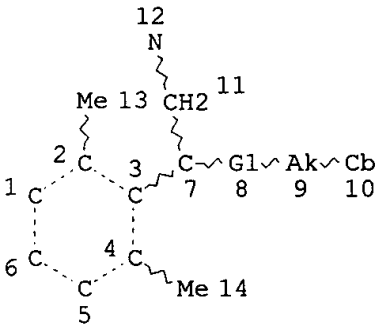


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GGCAT   IS MCY  UNS  AT  10
DEFAULT ECLEVEL IS LIMITED
ECOUNT  IS E6 C  AT  10

GRAPH ATTRIBUTES:
RSPEC   1
NUMBER OF NODES IS  14

STEREO ATTRIBUTES: NONE
L7             6 SEA FILE=REGISTRY SSS FUL L5
L8             3 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L7
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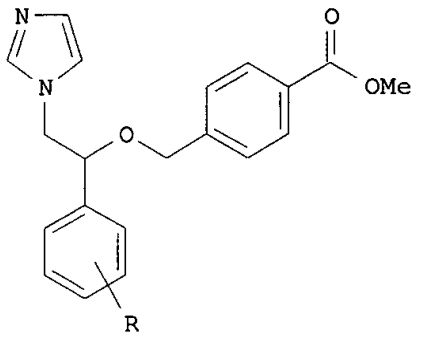
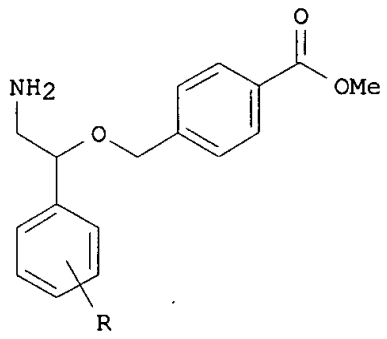
L8 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:487416 HCAPLUS
DN 125:247685
TI A solid-phase synthesis of miconazole analogs via an iodoetherification reaction
AU Tortolani, David R.; Biller, Scott A.
CS Bristol-Myers Squibb Pharm. Res. Inst., Princeton, NJ, 08543, USA
SO Tetrahedron Lett. (1996), 37(32), 5687-5690
CODEN: TELEAY; ISSN: 0040-4039
DT Journal
LA English
GI



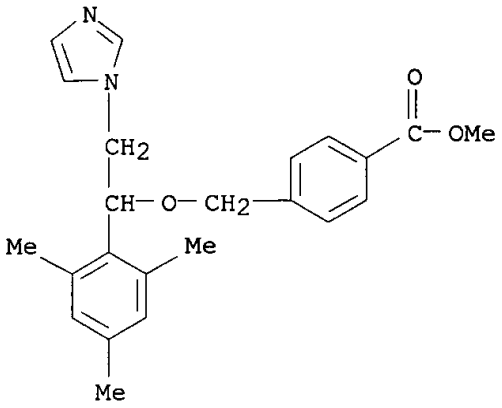
I



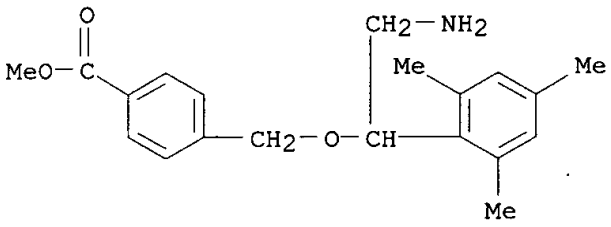
II

AB A procedure for the prepn. of various analogs of miconazole, I and II (R = 2,4,6-Me3, 3,5-F2, 4-cyclohexylphenyl, 3-Br, etc.), on solid support is described. A novel iodoetherification transformation is utilized as the key synthetic step. Thus, treatment of 4-(HOCH2)C6H4CO2CH2-X (X = polymer resin) with 2,4,6-Me3C6H2CH:CH2 and N-iodosuccinimide in the presence of triflic acid gave the iodoethyl ether 2,4,6-Me3C6H2CH(CH2I)OCH2C6H4CO2CH2-X, while underwent substitution reaction with (trimethylsilyl)imidazole and then resin cleavage to give I (R = 2,4,6-Me3). This approach has been applied to the combinatorial synthesis of 45 analogs.

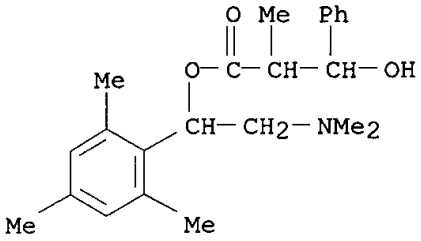
IT **182131-97-1P 182132-35-0P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(solid-phase synthesis of miconazole analogs via iodoetherification)
RN 182131-97-1 HCAPLUS
CN Benzoic acid, 4-[[2-(1H-imidazol-1-yl)-1-(2,4,6-trimethylphenyl)ethoxy]methyl]-, methyl ester (9CI) (CA INDEX NAME)



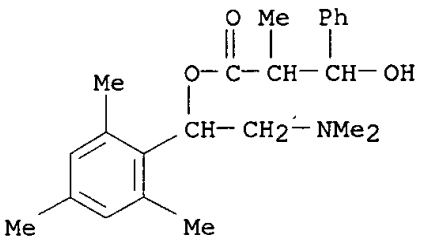
RN 182132-35-0 HCAPLUS
CN Benzoic acid, 4-[[2-amino-1-(2,4,6-trimethylphenyl)ethoxy]methyl]-, methyl ester (9CI) (CA INDEX NAME)



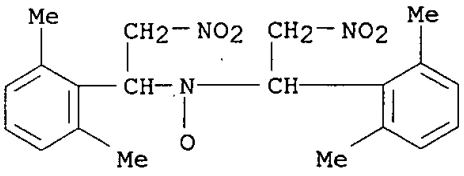
L8 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2002 ACS
AN 1990:440077 HCAPLUS
DN 113:40077
TI Auxiliary structure and asymmetric induction in the Mukaiyama-aldol reactions of chiral silyl ketene acetals
AU Gennari, Cesare; Molinari, Francesco; Cozzi, PierGiorgio; Oliva, Ambrogio
CS Dip. Chim. Org. Ind. Nat., Univ. Milano, Milan, 20133, Italy
SO Tetrahedron Lett. (1989), 30(38), 5163-6
CODEN: TELEAY; ISSN: 0040-4039
DT Journal
LA English
OS CASREACT 113:40077
AB A variety of chiral auxiliaries [e.g., (1S,2R-Me2NCHMeCHPhOH, (S)-Me2NCH2CHMeOH] were prepd. and tested for levels of asym. induction control in the Mukaiyama-aldol reaction of chiral silyl ketene acetals. Structural features required for high levels of control are discussed.
IT **127677-18-3P 127759-16-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)
RN 127677-18-3 HCAPLUS
CN Benzenepropanoic acid, .beta.-hydroxy-.alpha.-methyl-, 2-(dimethylamino)-1-(2,4,6-trimethylphenyl)ethyl ester, [.alpha.R-[.alpha.R*(S*),.beta.S*]]- (9CI) (CA INDEX NAME)



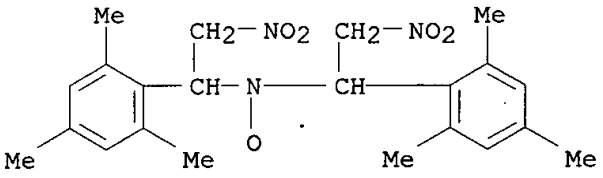
RN 127759-16-4 HCAPLUS
CN Benzenepropanoic acid, .beta.-hydroxy-.alpha.-methyl-, 2-(dimethylamino)-1-(2,4,6-trimethylphenyl)ethyl ester, [.alpha.R-[.alpha.R*(S*),.beta.R*]]- (9CI) (CA INDEX NAME)



L8 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2002 ACS
AN 1972:3004 HCAPLUS
DN 76:3004
TI Electron spin resonance study of nitroxides formed in the reaction of nitrogen dioxide and nitrogen oxide with styrenes
AU Jonkman, Leffert; Muller, Hans; Kommandeur, Jan
CS Lab. Phys. Chem., Univ. Groningen, Groningen, Neth.
SO J. Amer. Chem. Soc. (1971), 93(22), 5833-8
CODEN: JACSAT
DT Journal
LA English
AB When NO2 reacts with styrenes ACR:CH2 (A = Ph, 2,4,6-Me3C6H2; R = H, Me) in the presence of nitrosobenzene, phenyl(1-aryl-2-nitroethyl) nitroxides ACR(CH2NO2)N(O)Ph are formed through the reaction of .beta.-nitroalkyl radicals .bul.CARCH2NO2 (I) with nitrosobenzene. In the reaction of NO2-NO mixts. with styrenes, bis(1-aryl-2-nitroethyl) nitroxides ON(CARCH2NO2)2 (II) are formed by the reaction of I with the .alpha.-nitroso-.beta.-nitro addn. products ACR(NO)CH2NO2 (III) of the styrenes. Both diastereomers of II (meso, and d,l) were observed with all styrenes investigated, except for those with ortho substituents. Dissocn. of the dimer of III is accompanied by decompn. of III into NO and the radical I with subsequent formation of the nitroxide II.
IT **34818-06-9 34818-07-0**
RL: PRP (Properties)
(ESR of)
RN 34818-06-9 HCAPLUS
CN Nitroxide, bis[1-(2,6-dimethylphenyl)-2-nitroethyl] (9CI) (CA INDEX NAME)



RN 34818-07-0 HCAPLUS
CN Nitroxide, bis[2-nitro-1-(2,4,6-trimethylphenyl)ethyl] (9CI) (CA INDEX NAME)



Inventor Search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=> d que
L11         1400 SEA FILE=HCAPLUS ABB=ON  PLU=ON  FUCHS K?/AU OR STRANSKY W?/AU
                 OR GRAUERT M?/AU OR CARTER A?/AU OR GAIDA W?/AU OR WEISER
                 T?/AU OR ENSINGER H?/AU
L12           11 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L11 AND (ETHANOLAMIN? OR
                 ETHYLENEDIAMIN?)
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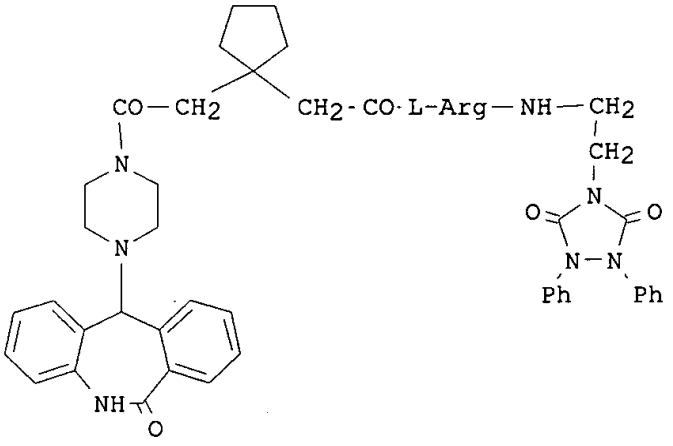
L12 ANSWER 1 OF 11 HCAPLUS COPYRIGHT 2002 ACS
AN 1999:684274 HCAPLUS
DN 131:286832
TI Preparation of novel peptides for use as NPY antagonists
IN Dollinger, Horst; Esser, Franz; Mihm, Gerhard; Rudolf, Klaus; Schnorrenberg, Gerd; **Gaida, Wolfram**; Doods, Henri Nico
PA Boehringer Ingelheim Pharma K.-G., Germany
SO Ger. Offen., 26 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI DE 19816929	A1	19991021	DE 1998-19816929	19980416

GI



I

AB Title compds. of the formula R1NC(O)-A-C(O)-B-G, where R, R1 = (independently) H, (un)substituted alkyl, heterocyclic ring, amino, or (un)substituted piperazine or hexahydro-1,4-diazepine; A = 3-6 atom (un)satd. (heterocyclic) spiro ring, an ortho-substituted (un)satd. (un)substituted cyclohexane, or CH2-W-CH2 where W = O, S, NR2; R2 = (phenyl)alkyl; B = (un)substituted D- or L-amino acid; G = alkoxy, (un)substituted amine, (un)substituted alkyl, or heterocyclic ring, were prepd. for pharmaceutical use as NPY antagonists in the treatment of coronary, cerebral, or renal vasospasm hyper- or hypotension, obesity, and bulimia. Thus (I.2 HCl) was prepd. using 11-(1-piperazino)-5,6-dihydro-6-oxo-morphanthridine, 3,3-tetramethylene-glutaric anhydride, L-arginine, and 4-(2-aminoethyl)-1,5-diphenyl-urazole (prepn. given). In in vitro receptor affinity tests using NPY receptor prepns. from rabbits, I had IC50 7.5x10-9 M.

L12 ANSWER 2 OF 11 HCAPLUS COPYRIGHT 2002 ACS
AN 1999:328754 HCAPLUS

DN 131:67145
TI Synthesis and structure of some cobalt(II), cobalt(III) and one nickel(II) monomeric, monodentate(S) thiosulfato complexes. Trans and cis structural effects in the cobalt(III) complexes
AU **Carter, Alan**; Drew, Michael G. B.
CS Department of Chemistry, Wellington College, Crowthorne, RG11 7PU, UK
SO Polyhedron (1999), 18(10), 1445-1453
CODEN: PLYHDE; ISSN: 0277-5387
PB Elsevier Science Ltd.
DT Journal
LA English
AB The crystal structures of five newly prepd. monomeric complexes with monodentate thiosulfato-S ligation were detd. (NH4)6[CoII(S2O3)4].cntdot.H2O (I) contains a novel [Co(II)(S2O3)4]6- anion in which the Co has a distorted tetrahedral coordination environment and is bonded to four discrete thiosulfate ligands: (Co-S, 2.330(3)-2.351(4) .ANG.). Trans-(NMe4)2[CoII(H2O)4(S2O3)2] (II) and trans-(NMe4)2[NiII(H2O)4(S2O3)2] (III) are isomorphous and contain trans-[MII(H2O)4(S2O3)2]2- [M = Co(II) and Ni(II)]. The anions are centrosym. with the metals in octahedral environments; [Co(II)-S, 2.488(2); Co(II)-O, 2.104(3), 2.120(3); Ni(II)-S, 2.452(1); Ni(II)-O, 2.080(2), 2.100(2) .ANG.]. Trans-Na[CoIII(en)2(S2O3)2] (IV) and trans-NH4[CoIII(en)2(S2O3)2].cntdot.2H2O (V) contain the trans-[CoIII(en)2(S2O3)2]1- anion with Na+ and NH4+ cations, resp. These anions are centrosym. with Co in an octahedral environment; [IV Co(III)-S, 2.340(3); Co-N, 1.982(6), 2.002(6); V Co(III)-S, 2.322(1); Co-N, 1.974(5) .ANG.]. In IV and V, there are structural trans effects; with mutually trans thiosulfato ligands, the Co(III)-thiosulfate bond is lengthened, by 0.061(3) and 0.043(2) .ANG. for IV and V, resp. This structural trans effect correlates with the general labilizing of ligands trans to thiosulfate ligands, but is not consistent with the stability of the anion in D and E to nucleophilic substitution. This stability is attributed to four intramol. H bonds (N-H.cntdot..cntdot..cntdot.O-S) between the **ethylenediamine** and thiosulfate ligands. In IV and V, the Co-N bond lengths cis to the thiosulfate ligand are slightly longer than expected: for IV by 0.041 and 0.021 .ANG., and in V by 0.013 .ANG.. This cis lengthening may be assocd. with the intramol. (N-H.cntdot..cntdot..cntdot.O-S) H bonds, but there is no direct correlation between the cis lengthening and the shortness of the H bond.
RE.CNT 32
RE
(1) Baggio, R; Acta Cryst 1975, VB31, P2359 HCAPLUS
(2) Bernhardt, P; Inorg Chem 1997, V36, P2420 HCAPLUS
(4) Cooper, J; Inorg Chem 1980, V19, P2265 HCAPLUS
(6) Cooper, J; Inorg Chem 1983, V22, P3060 HCAPLUS
(9) Ferrari, A; Acta Cryst 1966, V21, P605 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 3 OF 11 HCAPLUS COPYRIGHT 2002 ACS
AN 1993:12254 HCAPLUS
DN 118:12254
TI NMR study of the kinetics of ligand-exchange reactions of **ethylenediamine** with tetrakis(**ethylenediamine**)lanthanide(III) complexes
AU Forsberg, John H.; Dolter, Theodore J.; **Carter, Ann M.**; Singh, Deepak; Aubuchon, Steven A.; Timperman, Aaron T.; Ziaee, Ali
CS Dep. Chem., Saint Louis Univ., St. Louis, MO, 63103, USA

SO Inorg. Chem. (1992), 31(26), 5555-60
CODEN: INOCAJ; ISSN: 0020-1669
DT Journal
LA English
AB The kinetics of the exchange reactions of N-deuterated **ethylenediamine** with paramagnetic Ln(en-d4)43+ (Ln = Pr, Nd, Eu, Er, Yb) complexes in deuterated MeCN were studied at 233-343 K using 1H NMR. The data were analyzed by line shape anal. using the equation for a 2-site exchange. The mean ligand residence times, .tau.m, increased across the lanthanide series. The Er and Yb systems demonstrated both the slow- and fast-exchange limits over this temp. range on both the 300- and 100-MHz time scales; however, exchange involving complexes of the larger metal ions revealed coalescence of the coordinated and free ligand peaks even at the lowest temp. studied (233 K). A linear dependency of 1/.tau.m on the concn. of free ligand was obsd. for complexes derived from the larger ions (Pr, Nd, Eu), corresponding to a rate law that was 1st order in en concn. An A or Ia mechanism was proposed for these systems. For complexes of the small ions (Ln = Er, Yb), 1/.tau.m was independent of the **ethylenediamine** concn. at higher temps. and revealed a nonlinear dependency at lower temps. A limiting D mechanism was proposed for exchange involving complexes of the smaller ions at higher temps., whereas an Id pathway was proposed for these systems at lower temps.

L12 ANSWER 4 OF 11 HCAPLUS COPYRIGHT 2002 ACS
AN 1988:529067 HCAPLUS
DN 109:129067
TI Preparation of tetracyclic, fused-ring 1,4-diazepines as platelet-activating factor (PAF) antagonists
IN Weber, Karl Heinz; Harreus, Albrecht; **Stransky, Werner**; Walther, Gerhard; Casals, Stenzel Jorge; Muacevic, Gojko; Heuer, Hubert; Bechtel, Wolf Dietrich
PA Boehringer Ingelheim K.-G., Fed. Rep. Ger.
SO Ger. Offen., 68 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 3724031	A1	19880128	DE 1987-3724031	19870721
	EP 254245	A1	19880127	EP 1987-110443	19870718
	EP 254245	B1	19940928		
	R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	ES 2061452	T3	19941216	ES 1987-110443	19870718
	FI 8703180	A	19880123	FI 1987-3180	19870720
	PL 153970	B1	19910628	PL 1987-266884	19870720
	PL 157209	B1	19920529	PL 1987-287349	19870720
	DK 8703797	A	19880123	DK 1987-3797	19870721
	NO 8703041	A	19880125	NO 1987-3041	19870721
	NO 166942	B	19910610		
	NO 166942	C	19910918		
	JP 63033382	A2	19880213	JP 1987-182121	19870721
	JP 08005895	B4	19960124		
	ZA 8705333	A	19890329	ZA 1987-5333	19870721
	HU 50830	A2	19900328	HU 1987-3355	19870721
	HU 203354	B	19910729		
	DD 281389	A5	19900808	DD 1987-305190	19870721

	CS 274456	B2	19910411	CS 1987-5508	19870721
	CS 277445	B6	19930317	CS 1989-1930	19870721
	CS 277446	B6	19930317	CS 1989-1931	19870721
	AU 8776015	A1	19880128	AU 1987-76015	19870722
	AU 609408	B2	19910502		
	CA 1338287	A1	19960430	CA 1987-542748	19870722
	CZ 284052	B6	19980812	CZ 1989-2206	19890410
	SU 1738089	A3	19920530	SU 1989-4614791	19890817
	US 5532233	A	19960702	US 1994-302578	19940908
PRAI	DE 1986-3624647		19860722		
	US 1987-76515		19870722		
	US 1987-88758		19870824		
	US 1989-352527		19890516		
	US 1990-538582		19900614		
	US 1991-724654		19910702		
	US 1992-942556		19920909		
	US 1993-61392		19930513		

OS CASREACT 109:129067; MARPAT 109:129067

GI For diagram(s), see printed CA Issue.

AB The title compds. [I; R1 = H, cycloalkyl, halo, (un)substituted alkyl, alkoxy; R2 = H, halo, cyano, CHO, OH, etherified or esterified OH, alkylthio, (un)modified CO2H, amino, benzimidazolyl, (un)substituted 5-, 6-, or 7-membered heterocyclyl; R3 = pyridyl, (un)substituted Ph; R4 = H, alkyl, alkanoyl; R5 = H; R4R5 = bond; X, Y = R6C, N; R6 = R1, alkoxycarbonyl; Z = bond, C1-6 alkylene; A = fused, unsatd., (un)substituted 5-, 6-, or 7-membered ring] and their stereoisomers and physiol. acceptable salts were prepd. as PAF antagonists. Cyclopentathien otriazolodiazepinecarboxylate II (R7 = EtO) was prepd. in 7 steps, starting with cyclocondensation of Et 3-oxocyclopentanecarboxylate with 2-ClC6H4COCH2CN. The ester was sapond. to give II (R7 = OH) which was treated with morpholine and 1,1'-carbonyldiimidazole to give morpholide II (R7 = morpholine) (III). III inhibited blood platelet aggregation with an IC50 of 0.3 .mu.M and, in the benzodiazepine receptor binding test, had an IC50 of 3600 .times. 10-9 M. In the same tests triazolam had an IC50 of 9 .mu.M and 1.4 .times. 10-9 M, resp. III is thus expected to have little CNS activity.

L12 ANSWER 5 OF 11 HCAPLUS COPYRIGHT 2002 ACS

AN 1988:473485 HCAPLUS

DN 109:73485

TI Preparation and testing of azolobenzodiazepines as PAF antagonists

IN Walther, Gerhard; Harreus, Albrecht; Weber, Karl Heinz; **Stransky, Werner**; Muacevic, Gojko; Casals, Stenzel Jorge; Bechtel, Wolf Dietrich

PA Boehringer Ingelheim K.-G., Fed. Rep. Ger.

SO Ger. Offen., 26 pp.
CODEN: GWXXBX

DT Patent

LA German

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 3724164	A1	19880128	DE 1987-3724164	19870722
	SU 1681729	A3	19910930	SU 1987-4202929	19870720
	EP 255028	A2	19880203	EP 1987-110590	19870722
	EP 255028	A3	19900321		

R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE

	DD 266355	A5	19890329	DD 1987-305296	19870723
	DK 8703875	A	19880126	DK 1987-3875	19870724
	FI 8703243	A	19880126	FI 1987-3243	19870724
	NO 8703108	A	19880126	NO 1987-3108	19870724
	AU 8776103	A1	19880128	AU 1987-76103	19870724
	AU 603591	B2	19901122		
	JP 63035574	A2	19880216	JP 1987-185347	19870724
	HU 44788	A2	19880428	HU 1987-3414	19870724
	HU 197011	B	19890228		
	ZA 8705446	A	19890329	ZA 1987-5446	19870724

PRAI DE 1986-3625197 19860725
OS CASREACT 109:73485; MARPAT 109:73485
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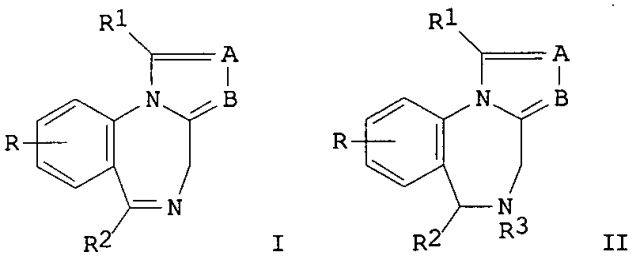


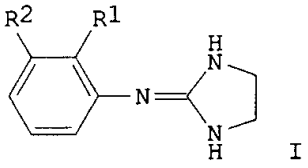
I II

AB The title compds. [I and II; R = OXCO2R4, OXCOR5, OYR6, ZCO2R4, ZCOR5, heterocyclylalkylene; R1 = H, alkyl, cycloalkyl, alkoxy, halo; R2 = (substituted) Ph, pyridiyl; R3 = H, alkyl; R4 = H, aminoalkyl, (hetero)cycloalkyl, alkyl; R5 = amino, heterocyclyl; R6 = amino, succinimido, phthalimido; A, B = N, CH, CMe; X, Y = alkylene; Z = alkylene, bond] were prepd. as platelet activating factor (PAF) antagonists. 8-Cyano-6-(2-chlorophenyl)-1-methyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine was treated with ethanolic HCl for 6 days in a refrigerator and the resulting imido ester was heated with H2NCH2CH2NH2 at 80.degree. for 3 h to give 6-(2-chloropheny)-8-(2-imidazolin-2-yl)-1-methyl-4H[1,2,4]triazolo[4,3-a][1,4]benzodiazepine. I and II inhibited PAF with IC50's of 0.1-1.3 .mu.M.

L12 ANSWER 6 OF 11 HCAPLUS COPYRIGHT 2002 ACS
AN 1988:33961 HCAPLUS
DN 108:33961
TI Conformational preference for the binding of biaryl substrates and inhibitors to the active site of phenylethanolamine N-methyltransferase (PNMT)
AU Grunewald, Gary L.; **Carter, Anne E.**; Sall, Daniel J.; Monn, James A.
CS Dep. Med. Chem., Univ. Kansas, Lawrence, KS, 66045, USA
SO J. Med. Chem. (1988), 31(1), 60-5
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
OS CASREACT 108:33961
AB Previously, regions of steric bulk tolerance in the arom. ring-binding site of PNMT (EC 2.1.1.28) for phenylethanolamine substrates and .alpha.-methylbenzylamine inhibitors were described. For bound

substrates, this region is located in the vicinity of the para position of the arom. ring, whereas in bound .alpha.-methylbenzylamine inhibitors, it is located in the region complementary to the meta position. In the present study, the preferred conformation of the biaryl portion of (m-phenylphenyl)- and p-(phenylphenyl)**ethanolamine** (I and II, resp.), as well as for m-phenyl- and p-phenyl-.alpha.-methylbenzylamine (III and IV, resp.) for PNMT active site interactions. Planar derivs. of I, II, III, and IV were obtained through the synthesis of 2-(1-fluoreny)-2-hydroxyethylamine (V), 2-(2-fluorenyl)-2-hydroxyethylamine (VI), 1-(1-fluorenyl)ethylamine (VII), and 1-(2-fluorenyl)ethylamine (VIII). The 4 fluorene derivs. were examd. for in vitro activity as substrates and inhibitors of the PNMT-catalyzed reaction. As in the case of I-IV, a positional preference for the alkylamine side chain was obsd. with respect to the biphenyl skeleton present in V-VIII. Thus, VI (p-biphenyl) displays a Km (26 .mu.M) that is .apprx.10-fold lower than that for V (m-biphenyl, Km = 297 .mu.M); in the .alpha.-methylbenzylamine inhibitors, fluorenyl deriv. VII (m-biphenyl, Ki = 4.14 .mu.M) is .apprx.40-fold better than VIII (p-biphenyl, Ki = 185 .mu.M) for in vitro inhibition of PNMT. In each case, conformational restriction of the biaryl system present in I-IV, such that the arom. rings are coplanar, resulted in enhanced affinity for the PNMT active site. Thus, conformational restriction of II (Km = 82 .mu.M) as in VI (Km = 26 .mu.M) and III (Ki = 89 .mu.M) as in VII (Ki = 4.14 .mu.M) leads, in each case, to a stronger enzyme-ligand dissociable complex. Thus, the PNMT active site beyond the zone that interacts with the central arom. ring portion of phenylethanolamine substrates and .alpha.-methylbenzylamine inhibitors is essentially a flat, hydrophobic pocket.

L12 ANSWER 7 OF 11 HCAPLUS COPYRIGHT 2002 ACS
AN 1985:160046 HCAPLUS
DN 102:160046
TI Structure-activity relationship in clonidine-like 2,3-disubstituted 2-aryliminoimidazolidines
AU Hoefke, W.; **Gaida, W.**; Staehle, H.
CS Dep. Pharmacol., Boehringer Ingelheim K.-G., Ingelheim/Rhein, D-6507, Fed. Rep. Ger.
SO Arzneim.-Forsch. (1985), 35(1A), 424-7
CODEN: ARZNAD; ISSN: 0004-4172
DT Journal
LA English
OS CASREACT 102:160046
GI



I

AB The hypotensive activity of 9 2,3-disubstituted 2-aryliminoimidazolidines I (R1 = Br, Cl, or Me; R2 = F, Cl, Br, or Me) was detd. in anesthetized rabbits. I with 3-Br substituents on the Ph moiety showed hypotensive activity that was more potent or equal to that of clonidine [4205-90-7].

There was a pos. correlation between the hypotensive activity of I and the partition coeff. between octanol and phosphate buffer and also between the I hypotensive activity and the max. .alpha.-adrenergic activity in spinalized rats. The correlation between I hypotensive activity and the neg. logarithm of the molar dose which caused a half max. increase in blood pressure in spinalized rats (an indication of the drug-receptor binding in vivo) was not so strong. There was no correlation between the acidity of I and the hypotensive activity.

L12 ANSWER 8 OF 11 HCAPLUS COPYRIGHT 2002 ACS
AN 1982:199711 HCAPLUS
DN 96:199711
TI 3,1-Benzoxazin-2-ones and their uses
IN Mentrup, Anton; Schromm, Kurt; Renth, Ernst Otto; Hoefke, Wolfgang; **Gaida, Wolfram**; Streller, Ilse; Fuegner, Armin
PA Boehringer, C. H., Sohn, Fed. Rep. Ger.
SO Eur. Pat. Appl.
CODEN: EPXXDW
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 43940	A1	19820120	EP 1981-104787	19810622
	EP 43940	B1	19840912		
	R: AT, BE, CH, DE, FR, IT, LU, NL, SE				
	DE 3026534	A1	19820318	DE 1980-3026534	19800712
	AT 9336	E	19840915	AT 1981-104787	19810622
	US 4341778	A	19820727	US 1981-280349	19810706
	DK 8103067	A	19820113	DK 1981-3067	19810710
	DK 149851	B	19861013		
	DK 149851	C	19870504		
	FI 8102183	A	19820113	FI 1981-2183	19810710
	FI 74703	B	19871130		
	FI 74703	C	19880310		
	NO 8102355	A	19820113	NO 1981-2355	19810710
	NO 158578	B	19880627		
	NO 158578	C	19881005		
	GB 2080296	A	19820203	GB 1981-21321	19810710
	GB 2080296	B2	19830928		
	ES 503837	A1	19820601	ES 1981-503837	19810710
	AU 8172731	A1	19820916	AU 1981-72731	19810710
	AU 540916	B2	19841206		
	ZA 8104687	A	19830330	ZA 1981-4687	19810710
	DD 202018	A5	19830824	DD 1981-231670	19810710
	HU 25946	O	19830829	HU 1981-2036	19810710
	HU 183515	B	19840528		
	CA 1165317	A1	19840410	CA 1981-381559	19810710
	IL 63285	A1	19850331	IL 1981-63285	19810710
	JP 57048975	A2	19820320	JP 1981-109186	19810713
	ES 508653	A1	19821101	ES 1982-508653	19820112
	ES 508654	A1	19821101	ES 1982-508654	19820112
	ES 508655	A1	19821101	ES 1982-508655	19820112
PRAI	DE 1980-3026534		19800712		
	EP 1981-104787		19810622		

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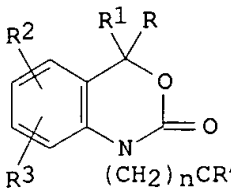

I

AB Benzoxazinones I (R, R1, R6 = H, alkyl; R2, R3 = H, F, Cl, OH, Me, Et, alkoxy; R2R3 = OCH2O; R4, R5 = H, Me; R7 = substituted Ph; n = 1-3) were prepd. Thus 1,1-dimethyl-3-(4,4-dimethyl-2-oxo-3,1-benzoxazin-1-yl)propanamine was treated with 3,4-H2NCO(HO)C6H3COCH2Br and reduced with NaBH4 to give I [R = R1 = R4 = R5 = Me, R2 = R3 = R6 = H, R7 = 3,4-H2NCO(HO)C6H3, n = 2](II). II.MeSO3H had antihypertensive activity at 10 mg/kg orally in rats.

L12 ANSWER 9 OF 11 HCAPLUS COPYRIGHT 2002 ACS
AN 1982:35255 HCAPLUS
DN 96:35255
TI 2-(3,5-Dibromo-4-amino-phenylimino)-imidazolidine, its salts and compositions
IN Staehle, Helmut; Koeppe, Herbert; Kummer, Werner; Hoefke, Wolfgang; **Gaida, Wolfram**; Pichler, Ludwig
PA Boehringer Ingelheim G.m.b.H., Fed. Rep. Ger.
SO U.S., 3 pp. Cont.-in-part of U.S. 4,250,186.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 4293564	A	19811006	US 1980-179839	19800820
	DE 2806775	A1	19790830	DE 1978-2806775	19780217
	US 4250186	A	19810210	US 1979-12650	19790216
PRAI	DE 1978-2806775		19780217		
	US 1979-12650		19790216		

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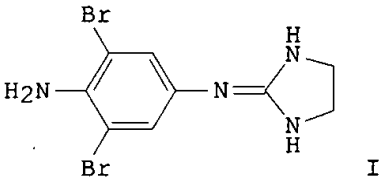

I

AB The bradycardiac title compd. (I) was prepd. Thus, 30.35 g 2-(4-amino-3,5-dibromophenyl)-methylisothiouronium hydriodide was treated with 6.5 g H2NCH2CH2NH2 in MeOH to give 13.3% I.HCl. At 1 mg/kg I reduced the heart beat of rabbits by 202 beats/min.

L12 ANSWER 10 OF 11 HCAPLUS COPYRIGHT 2002 ACS

AN 1980:41946 HCAPLUS
DN 92:41946
TI Substituted 2-phenyliminoimidazolidines and their acid addition salts
IN Staehle, Helmut; Koeppe, Herbert; Kummer, Werner; Hoefke, Wolfgang; **Gaida, Wolfram**; Pichler, Ludwig
PA Boehringer, C. H., Sohn, Fed. Rep. Ger.
SO Ger. Offen., 18 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 2806775	A1	19790830	DE 1978-2806775	19780217
	SU 812175	A3	19810307	SU 1979-2721602	19790209
	AT 7901015	A	19820715	AT 1979-1015	19790212
	AT 370093	B	19830225		
	RO 81504	P	19830429	RO 1979-103172	19790213
	CH 640230	A	19831230	CH 1979-1428	19790214
	FI 7900510	A	19790818	FI 1979-510	19790215
	FI 69301	B	19850930		
	FI 69301	C	19860110		
	DD 142048	C	19800604	DD 1979-211044	19790215
	IL 56678	A1	19820131	IL 1979-56678	19790215
	HU 22938	O	19820728	HU 1979-BO1764	19790215
	HU 180430	B	19830328		
	BE 874252	A1	19790816	BE 1979-193531	19790216
	DK 7900694	A	19790818	DK 1979-694	19790216
	NO 7900523	A	19790820	NO 1979-523	19790216
	NO 151239	B	19841126		
	NO 151239	C	19850306		
	NL 7901241	A	19790821	NL 1979-1241	19790216
	AU 7944325	A1	19790823	AU 1979-44325	19790216
	AU 519356	B2	19811126		
	GB 2014575	A	19790830	GB 1979-5506	19790216
	GB 2014575	B2	19821110		
	FR 2417502	A1	19790914	FR 1979-4052	19790216
	FR 2417502	B1	19810626		
	JP 54122273	A2	19790921	JP 1979-17156	19790216
	ES 477784	A1	19800401	ES 1979-477784	19790216
	ZA 7900709	A	19801029	ZA 1979-709	19790216
	US 4250186	A	19810210	US 1979-12650	19790216
	PL 115759	B1	19810430	PL 1979-213475	19790216
	PL 116527	B1	19810630	PL 1979-221508	19790216
	CA 1115717	A1	19820105	CA 1979-321805	19790216
	RO 76799	P	19810530	RO 1979-96602	19790217
	CS 207773	P	19810831	CS 1979-1092	19790219
	CS 207774	P	19810831	CS 1979-8500	19790219
	ES 485043	A1	19800516	ES 1979-485043	19791016
	SU 828964	A3	19810507	SU 1980-2874805	19800130
	US 4293564	A	19811006	US 1980-179839	19800820
PRAI	DE 1978-2806775		19780217		
	US 1979-12650		19790216		

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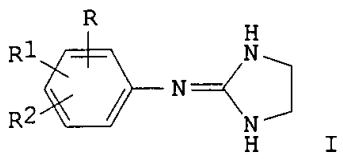

I

AB The title compds. I (R = Br, Cl, OH, SMe; R1 = H, OH, F, Br; R2 = H, OH, Me, CH2OH, NH2) were prepd. for use in treatment of coronary disease (no data). Thus, 3-MeSC6H4NHC(SMe):NH.HI was refluxed with H2NCH2CH2NH2 in MeOH, followed by treatment with NaOH to give I (R = 3-MeS, R1 = R2 = H), isolated as the hydrobromide.

L12 ANSWER 11 OF 11 HCAPLUS COPYRIGHT 2002 ACS
AN 1978:509475 HCAPLUS
DN 89:109475
TI Pharmaceutical 2-bromo-3-chloro-N-2-imidazolidinylenebenzamine and its acid addition salts
IN Staehle, Helmut; Hoefke, Wolfgang; **Gaida, Wolfram**; Stockhaus, Klaus; Boeke, Karin
PA Boehringer, C. H., Sohn, Ger.
SO Ger. Offen., 9 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 2658808	A1	19780706	DE 1976-2658808	19761224
	FI 7703559	A	19780625	FI 1977-3559	19771124
	ZA 7707198	A	19790829	ZA 1977-7198	19771205
	SU 679139	D	19790805	SU 1977-2557053	19771219
	DD 133944	C	19790131	DD 1977-202895	19771222
	AU 7731872	A1	19790628	AU 1977-31872	19771222
	BE 862305	A1	19780623	BE 1977-183833	19771223
	DK 7705777	A	19780625	DK 1977-5777	19771223
	SE 7714750	A	19780625	SE 1977-14750	19771223
	NL 7714352	A	19780627	NL 1977-14352	19771223
	NO 7704445	A	19780627	NO 1977-4445	19771223
	JP 53079867	A2	19780714	JP 1977-155452	19771223
	FR 2375217	A1	19780721	FR 1977-39050	19771223
	ES 465368	A1	19780916	ES 1977-465368	19771223
	ES 469554	A1	19781201	ES 1978-469554	19780508
	ES 469555	A1	19781201	ES 1978-469555	19780508
	ES 469553	A1	19781201	ES 1978-469553	19780508
	ES 469551	A1	19781201	ES 1978-469551	19780508
	ES 469552	A1	19781201	ES 1978-469552	19780508
PRAI	DE 1976-2658808		19761224		

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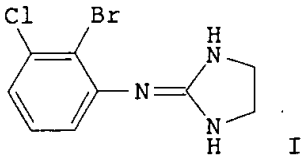

I

AB The antihypertensive title compd. I was prepd. in 71.3% yield by the reaction of an isothiuronium salt, e.g., 2,3-BrClC6H3NHC(SMe):NH.HI with H2NCH2CH2NH2. Eleven salts were also prepd. I.HCl at 0.035 mg/kg lowered the blood pressure in rabbits by 20 mm for 180 min, compared to 0.01 mg/kg and 80 min for Clonidine-HCl.